JAMA | Original Investigation

Effect of Continuous Infusion of Hypertonic Saline vs Standard Care on 6-Month Neurological Outcomes in Patients With Traumatic Brain Injury
The COBI Randomized Clinical Trial

Antoine Roquilly, MD, PhD; Jean Denis Moyer, MD; Olivier Huet, MD, PhD; Sigismond Lasocki, MD, PhD; Benjamin Cohen, MD; Claire Dahyot-Fizelier, MD, PhD; Kevin Chalard, MD; Philippe Seguin, MD, PhD; Caroline Jeantrelle, MD; Véronique Vermeersch, MD; Thomas Gaillard, MD; Raphael Cinotti, MD; Dominique Demeure dit Latte, MD; Pierre Joachim Mahe, MD; Mickael Vourc'h, MD; Florian Pierre Martin, MD; Alice Chopin, MD; Celine Lerebourg, MSc; Laurent Flet, PharmD; Anne Chiffoleau, MD; Fanny Feuillet, PhD; Karim Asehnoune, MD, PhD; for the Atlanrea Study Group and the Société Française d'Anesthésie Réanimation (SFAR) Research Network

IMPORTANCE Fluid therapy is an important component of care for patients with traumatic brain injury, but whether it modulates clinical outcomes remains unclear.

OBJECTIVE To determine whether continuous infusion of hypertonic saline solution improves neurological outcome at 6 months in patients with traumatic brain injury.

DESIGN, SETTING, AND PARTICIPANTS Multicenter randomized clinical trial conducted in 9 intensive care units in France, including 370 patients with moderate to severe traumatic brain injury who were recruited from October 2017 to August 2019. Follow-up was completed in February 2020.

INTERVENTIONS Adult patients with moderate to severe traumatic brain injury were randomly assigned to receive continuous infusion of 20% hypertonic saline solution plus standard care (n = 185) or standard care alone (controls; n = 185). The 20% hypertonic saline solution was administered for 48 hours or longer if patients remained at risk of intracranial hypertension.

MAIN OUTCOMES AND MEASURES The primary outcome was Extended Glasgow Outcome Scale (GOS-E) score (range, 1-8, with lower scores indicating worse functional outcome) at 6 months, obtained centrally by blinded assessors and analyzed with ordinal logistic regression adjusted for prespecified prognostic factors (with a common odds ratio [OR] >1.0 favoring intervention). There were 12 secondary outcomes measured at multiple time points, including development of intracranial hypertension and 6-month mortality.

RESULTS Among 370 patients who were randomized (median age, 44 [interquartile range, 27-59] years; 77 [20.2%] women), 359 (97%) completed the trial. The adjusted common OR for the GOS-E score at 6 months was 1.02 (95% CI, 0.71-1.47; *P* = .92). Of the 12 secondary outcomes, 10 were not significantly different. Intracranial hypertension developed in 62 (33.7%) patients in the intervention group and 66 (36.3%) patients in the control group (absolute difference, −2.6% [95% CI, −12.3% to 7.2%]; OR, 0.80 [95% CI, 0.51-1.26]). There was no significant difference in 6-month mortality (29 [15.9%] in the intervention group vs 37 [20.8%] in the control group; absolute difference, −4.9% [95% CI, −12.8% to 3.1%]; hazard ratio, 0.79 [95% CI, 0.48-1.28]).

CONCLUSIONS AND RELEVANCE Among patients with moderate to severe traumatic brain injury, treatment with continuous infusion of 20% hypertonic saline compared with standard care did not result in a significantly better neurological status at 6 months. However, confidence intervals for the findings were wide, and the study may have had limited power to detect a clinically important difference.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03143751

Visual Abstract

Supplemental content

CME Quiz at jamacmelookup.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Antoine Roquilly, MD, PhD, CHU de Nantes, Service d'anesthésie réanimation chirurgicale, Hôtel Dieu-HME, 5 allée de l'ile Gloriette, Nantes 4400, France (antoine.roquilly@chu-nantes.fr).

JAMA. 2021;325(20):2056-2066. doi:10.1001/jama.2021.5561

© 2021 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Mexico | Access Provided by JAMA , Caro Nolasco on 10/29/2024

SHOUT
SHARE
IT

In 2019, it was estimated that each year, 69 million individuals experience traumatic brain injury (TBI) from all causes worldwide.[1] The risk of mortality after TBI has steadily decreased in the last few decades, but the rate of incomplete recovery remains high, estimated to cause more than 8 million years of life lived with severe disability in 2016.[2,3] The morbidity, mortality, and long-term consequences associated with TBI have encouraged the evaluation of new practices to improve clinical outcomes.[4]

Fluid therapy is a major component of the prevention and treatment of secondary brain injuries that rapidly develop and dampen neurological recovery after trauma.[5] Although hypotonic solutions are not recommended in neuro-intensive care,[6] several teams have reported use of continuous infusion of hypertonic saline solutions, which results in sustained blood hyperosmolarity, either to prevent[7-10] or to treat[11] posttraumatic intracranial hypertension. Prophylactic continuous hypertonic therapy was shown to decrease the risk of intracranial hypertension in a phase 2 randomized clinical trial[12] and was associated with higher hospital survival in a systematic review of the literature.[13] However, the implicit disadvantage of continuous prophylactic infusions is that some patients who were never going to develop intracranial hypertension requiring any hyperosmolar therapy receive infusions and their consequent risks.

Continuous prophylactic hyperosmolar therapy is not recommended as resuscitation fluids in neuro-intensive care because data on its effects on long-term clinical outcomes are scarce.[6] The Continuous Hyperosmolar Therapy for Traumatic Brain-Injured Patients (COBI) trial was conducted to test the hypothesis in a randomized clinical trial that continuous infusion of 20% hypertonic saline solution improves neurological outcome at 6 months in patients with moderate to severe TBI.

Key Points

Question What is the effect of continuous infusion of hypertonic saline solution in patients with traumatic brain injury?

Findings In this randomized clinical trial that included 370 adults with moderate to severe traumatic brain injury, treatment with continuous infusion of 20% hypertonic saline vs standard care resulted in an odds ratio for better neurological outcomes (based on the Extended Glasgow Outcome Scale) of 1.02 after 6 months; this was not statistically significant.

Meaning Among patients with moderate to severe traumatic brain injury, treatment with continuous infusion of 20% hypertonic saline compared with standard care did not result in a significantly better neurological status at 6 months.

Methods

Design

We conducted an investigator-initiated multicenter, parallel-group, open-label, randomized clinical trial with blinded adjudication of the primary outcome to investigate the effects of continuous infusion of hypertonic saline solution in addition to standard care in patients with moderate to severe TBI. The study protocol was published before the first patient's inclusion in the study[14] and is available in Supplement 1.

Ethics

The study protocol was approved by the Ethics Committee of Ile de France VIII in May 2017. This trial was conducted according to the Declaration of Helsinki.[15] Written consent for participation was provided by patients' legal surrogates as soon as possible. Patients were eligible to be enrolled before the provision of legal surrogate consent if next of kin could not be informed within the maximum delay time for inclusion. Patients who had recovered sufficient capacity to provide consent were asked to consent to continue in the trial up to 6 months after the trauma event.

Trial Sites and Study Population

The study was conducted in intensive care units (ICUs) at 9 French university hospitals, each center caring for more than 50 TBI patients every year. Patients aged 18 to 80 years, admitted to the participating ICUs for moderate to severe TBI, defined as the association of a Glasgow Coma Scale score of 12 or lower (considering the worst score before sedation during the first 24 hours) together with traumatic abnormal brain computed tomography findings (extradural hematoma, subdural hematoma, subarachnoid hemorrhage, brain contusion, brain hematoma, brain edema, or skull fracture), were eligible in the first 24 hours after the trauma event. Noninclusion criteria were pregnancy (legal obligation); dependence on daily activity before trauma, association with a cervical spinal cord injury that would have affected the Extended Glasgow Outcome Scale [GOS-E] evaluation independent of brain function), imminent death or fixed dilated pupils with a score of 3 on the Glasgow Coma Scale (considered moribund), and fluid retention (ascites or pulmonary edema, considered a contraindication of sodium administration).

Randomization

Randomization was performed through a secure web-based randomization system. The randomization list was generated by a statistician not involved in determining eligibility or assessment of outcomes. Patients were randomized to receive continuous infusion of 20% hypertonic saline solution plus standard care (intervention group) or standard care alone (control group) (**Figure 1**) in fixed blocks of 6, in a 1:1 ratio, with stratification based on trauma severity (Glasgow Coma Scale score of 3-8 vs 9-12), which is a risk factor for poor neurological outcome at 6 months, and on whether a patient was administered a bolus of hyperosmolar therapy before inclusion in the study, which could interact with the study intervention.

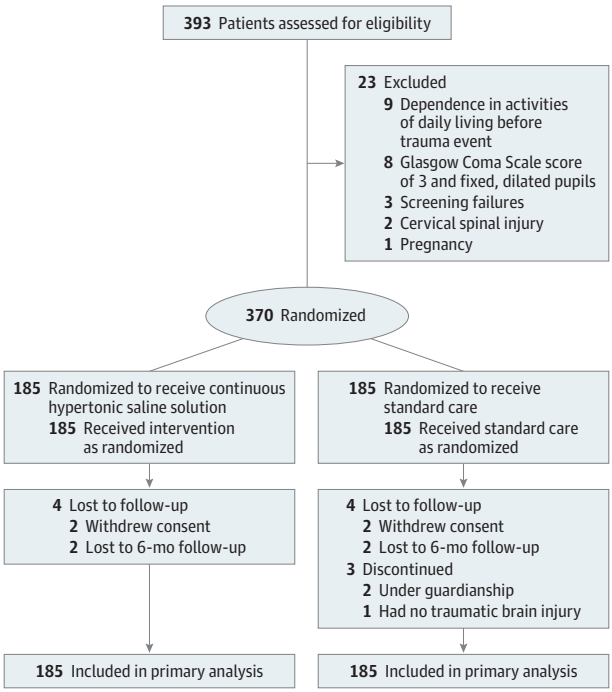
Continuous Infusion of 20% Hypertonic Saline Solution

Within 24 hours after trauma, a 1-hour bolus infusion (dose adapted to the basal blood level of sodium) was injected immediately after randomization. Continuous infusion of 20% hypertonic saline solution was administered (0.5-1 g/h of NaCl) and adapted to patients' serum sodium levels to limit the risk

© 2021 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Mexico | Access Provided by JAMA , Caro Nolasco on 10/29/2024

Figure 1. Flow of Participants Through the Continuous Hyperosmolar Therapy for Traumatic Brain-Injured Patients (COBI) Trial


393 Patients assessed for eligibility
23 Excluded
9 Dependence in activities of daily living before trauma event
8 Glasgow Coma Scale score of 3 and fixed, dilated pupils
3 Screening failures
2 Cervical spinal injury
1 Pregnancy
370 Randomized
185 Randomized to receive continuous hypertonic saline solution
185 Received intervention as randomized
185 Randomized to receive standard care
185 Received standard care as randomized
4 Lost to follow-up
2 Withdrew consent
2 Lost to 6-mo follow-up
4 Lost to follow-up
2 Withdrew consent
2 Lost to 6-mo follow-up
3 Discontinued
2 Under guardianship
1 Had no traumatic brain injury
185 Included in primary analysis
185 Included in primary analysis

Data for the primary outcome at 6 months were available for 359 patients (97%; 181 in the continuous hyperosmolar therapy group and 178 in the control group). Data at 3 months were available for 175 and 176 patients, respectively.

of severe hypernatremia (defined as Na^+ >155 mmol/L). The blood level of sodium was monitored every 8 hours for dose adaptation (eFigure 1 in Supplement 2). The intervention was continued for a minimum of 48 hours and as long as a patient was considered at risk of intracranial hypertension. The 20% NaCl infusion was stopped when all specific therapies against intracranial hypertension (stage 3 therapies; eFigure 2 in Supplement 2) were suspended for 12 hours or more. After the intervention cessation, spontaneous normalization of the blood level of sodium was monitored every 8 hours for 48 hours. During this period, a 1-hour bolus infusion (5 g) was injected if the sodium level was less than 140 mmol/L or decreased more than 12 mmol/L per day.[16] No hypotonic solution was administered to accelerate natremia normalization.

Standard Care

To avoid extreme differences in practice, site medical teams agreed to apply the revised Brain Trauma Foundation guidelines for standard treatment.[5,17] Isotonic crystalloid solutions were used as maintenance fluids and first-line resuscitation fluids in case of low blood pressure.[6] In case of intracranial hypertension, the 2 groups received standard treatment, potentially including boluses of sedative drugs and hyperosmolar therapy (200-250 mOsm of mannitol or hypertonic saline), moderate hypothermia, cerebrospinal fluid drainage, ventilation therapy, or decompressive craniectomy (eFigure 2 in Supplement 2). Continuous hyperosmolar therapy was allowed in the control group as rescue therapy for intracranial hypertension refractory to other therapies. In this case, patients were to be analyzed as part of the control randomization group.

Outcomes

The primary outcome was the GOS-E score at 6 months after the trauma event. It was not possible to blind local investigators and families to randomization group. The 3- and 6-month structured interviews were performed by telephone by trained research assistants from the coordinating center who were neither involved in patient recruitment and treatment nor aware of patients' randomized group in an effort to ensure blinding of the primary outcome assessment.[18,19] The GOS-E was scored based on telephone interviews conducted according to a standardized approach for which the reliability compared with an in-person test and French translation had been validated by others.[19-21] The 8-point scale assesses the autonomy of patients in daily activity. A GOS-E score of 1 indicates death; 2, vegetative state: inability to obey commands and speechlessness; 3, lower end of severe disability: dependence on others for care; 4, upper end of severe disability: partial independence at home; 5, lower end of moderate disability: inability to work; 6, upper end of moderate disability: reduced work capacity; 7, lower end of good recovery: ability to resume previous activities with some injury-related problems; and 8, upper end of good recovery: absence of trauma-related problems. An independent clinician was consulted in rare cases in which adjudication was required.

The following secondary outcomes were recorded: mortality at 6 months; GOS-E score at 3 months; duration of posttraumatic amnesia evaluated at ICU discharge, 3 months, and 6 months (Galveston Orientation and Amnesia Test <75/100); autonomy in activities of daily living at 3 and 6 months (Katz Index of Independence in Activities of Daily Living >6); quality of life, estimated by the Short Form 36 health survey at 3 months and 6 months (self-questionnaire); place of residence at 3 months and 6 months; evolutions of serum sodium level and blood osmolarity every 8 hours and daily, respectively (maximum, first 7 days and up to 2 days after treatment cessation); and intracranial pressure every 8 hours if available (maximum, first 7 days and up to 2 days after treatment cessation). No extrapolation of intracranial pressure values was performed in patients without intracranial pressure probes, who were considered to be free of intracranial hypertension. Levels of chlorine, potassium, and creatinine and pH during treatment (every 8 hours for 7 days and up to 2 days after treatment cessation) were recorded for an ancillary study and are not reported herein. The intensity of the management of intracranial hypertension was estimated by the frequency of episodes of intracranial hypertension (pressure >22 mm Hg for more than 20 minutes); the frequencies and durations of hyperosmolar therapy, therapeutic hypothermia, barbiturate coma, moderate hypocapnia, and external ventricular drainage; the frequency of decompressive craniectomy; and the frequency of kidney failure (Kidney Disease: Improving Global Outcomes [KDIGO] score of 2-3), severe thromboembolic accident (pulmonary embolism) without paraclinical

© 2021 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Mexico | Access Provided by JAMA , Caro Nolasco on 10/29/2024

systematic screening, and incidence of centropontine myelinolysis without paraclinical systematic screening.

Study Monitoring and Oversight

The study was monitored on behalf of the sponsor (Nantes University Hospital). Study initiation visits were performed before recruitment commenced. During regular monitoring visits, independent, experienced research staff carried out source data verification of trial data, monitored data integrity in all of the participating centers, and verified all informed consent forms. Expected and unexpected serious adverse events were reported in a blinded manner to the sponsor for central validation of their severity level, relation to the intervention, and whether they were expected. An independent data and safety monitoring board, appointed by the sponsor, oversaw ethics according to the Declaration of Helsinki,[15] regularly reviewed patient safety, and made recommendations to the sponsor about continuation, modification, or termination of the research.

Sample Size Calculation

Using an ordinal analysis increases the statistical efficiency of the analysis compared with the comparison of a categorical outcome.[22] As previously described by others,[23,24] we thus based the study calculation on a categorical outcome (the rate of poor neurological outcome, defined as a GOS-E score of 1-5) without reducing the number of patients to increase the statistical power of this study. In previous studies, continuous infusion of hypertonic saline solutions induced a relative reduction of mortality of 20%[13] and of intracranial hypertension of 30%,[12] and we thus hypothesized that it would induce a similar relative reduction of 20% in the rate of poor neurological outcome. Assuming a 70% rate of poor neurological outcome in the control group[18] and thus 56% in the intervention group (a relative decrease of 20%), we calculated that a total of 370 patients (185 patients per group) was needed to detect this difference with an $\alpha = .05$ type I error and a power of 80% in a 2-sided test.

Statistical Analysis

Patients were analyzed according to their randomization group. The analysis set includes all randomized patients. For management of missing data, analysis of the primary outcome was performed by multiple imputation methods (number of imputations: 10; relative efficiency >99%). The relationships between all baseline variables and the primary outcome as well as the treatment group were tested using χ^2 or *t* tests. The final multiple imputation model was based on age, sex, Glasgow Coma Scale score, boluses of hyperosmolar therapy and mannitol use before randomization, Marshall computed tomography classification, neurosurgery before inclusion (decompressive craniectomy, craniotomy for intracerebral hematoma), time from trauma event to randomization, stratification factors, and GOS-E score at 3 months.

The primary outcome measure (GOS-E score at 6 months) was analyzed with an ordinal method based on the proportional odds model. A likelihood ratio test was used to test the goodness of fit of the unadjusted proportional odds models. The nonrejection of the proportional odds model at the 5% significance level indicated similar GOS-E distributions between the 2 randomized groups and enabled the representation of the result as a common odds ratio (OR) with associated 95% confidence intervals. Following international recommendations, the proportional odds model was adjusted for key baseline covariates (age, Glasgow Coma Scale score, pupillary reactivity, hypotension, hypoxia, and brain computed tomography classification), for covariates used for the stratification of the randomization (trauma severity and administration of a bolus of hyperosmolar therapy before inclusion), and centers.[25,26] For this analysis and as previously described[23] we collapsed the 8-point GOS-E to 7 categories by pooling lower severe disability and vegetative state. This was done to avoid favoring an intervention that reduced the risk of death but increased the proportion of severe disability.

In prespecified subgroup analyses, we compared the proportions of patients with favorable outcome, defined as a GOS-E score of 6 to 8 at 6 months, using an adjusted logistic regression with the same adjustment variables as the primary analysis: severe vs moderate TBI (Glasgow Coma Scale score of 3-8 vs 9-12), receipt of boluses of hyperosmolar therapy before inclusion, neurosurgical procedure before inclusion, blood sodium level before inclusion (<138, 138-145, or >145 mmol/L), pupil reactivity (both reacting vs one or both not reacting), age (<40, 40-60, or >60 years), time between trauma event and study inclusion (<8, 8-16, or >16 hours), and Marshall computed tomography score (diffuse injury vs mass lesion). As a post hoc analysis, we also investigated the subgroups of patients with and without elevated intracranial pressure prior to intervention initiation (≤22 mm Hg or >22 mm Hg) and the variation of treatment effect across hospitals. Heterogeneity in treatment effects across subgroups was assessed via χ^2 or Fisher exact tests.

Analyses of secondary outcomes were adjusted for covariates used for stratification as fixed effects (preplanned) and centers as a random effect (post hoc). Missing data are described by treatment group. The GOS-E score at 3 months was analyzed using the same ordinal method as described above for the primary outcome. Categorical data were analyzed using logistic regression models, and goodness of fit was tested using the Hosmer-Lemeshow statistic. Short Form 36 data were analyzed by dimension using linear regression models, and predicted values were used to assess normality assumption. The time courses of the blood levels of sodium, plasma osmolarity, and intracranial pressure and cerebral perfusion pressure values were analyzed by linear mixed-effects models with a random effect for patients. Continuous time, intervention vs control group, intervention × time interaction, and covariates used for stratification were included as fixed effects. The rates of death in a time-to-event analysis were calculated via Kaplan-Meier plots and were analyzed using Cox regression models.

Continuous variables are presented as means and standard deviations or as medians and interquartile ranges, and categorical data are presented as counts and percentages. Missing data are described by treatment group. Analyses were

© 2021 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Mexico | Access Provided by JAMA , Caro Nolasco on 10/29/2024

Table 1. Baseline Participant Characteristics

Characteristics	Intervention (n = 185)	Control (n = 185)
Age, median (IQR), y	46 (27-60) [n = 184]	43 (27-59) [n = 183]
Sex, No./total (%)		
Male	145/184 (78.8)	148/183 (80.9)
Female	39/184 (21.2)	35/183 (19.1)
Severe traumatic brain injury (GCS score ≤8), No./total (%)	134/184 (72.8)	131/183 (71.6)
GCS score, median (IQR)[a]	7 (4-9) [n = 184]	7 (4-9) [n = 184]
Motor response ≤5, No./total (%)	168/184 (91.3)	164/184 (89.6)
Pupillary response, No./total (%)[b]		
Both reacting	130/184 (70.7)	123/182 (67.6)
One reacting	42/184 (22.8)	47/182 (25.8)
None reacting	12/184 (6.5)	12/182 (6.6)
Hypotension, No./total (%)[c]	30/184 (16.3)	27/182 (14.8)
Hypoxia, No./total (%)[c]	29/184 (15.8)	26/182 (14.3)
Hemoglobin level <9.0 g/L before randomization, No./total (%)	14/184 (7.6)	15/182 (8.2)
Marshall CT classification, No./total (%)[d]		
I: diffuse injury, no visible intracranial pathology	7/184 (3.8)	4/182 (2.2)
II: diffuse injury, midline shift of 0-5 mm	78/184 (42.4)	90/182 (49.5)
III: diffuse injury, basal cisterns compressed/effaced	17/184 (9.2)	11/182 (6)
IV: diffuse injury, midline shift >5 mm	15/184 (8.2)	12/182 (6.6)
V: evacuated mass lesion	46/184 (25)	27/182 (14.8)
VI: nonevacuated mass lesion	21/184 (11.4)	38/182 (20.9)
Received bolus of hyperosmolar therapy prior to randomization, No./total (%)	103/184 (56)	101/182 (55.2)
Neurosurgery prior to randomization, No./total (%)	59/184 (32.1)	40/182 (22.0)
Intracranial pressure probe at randomization, No./total (%)	122/184 (66.3)	128/181 (70.7)
Intracranial pressure probe during ICU stay, No./total (%)	153/184 (83.2)	163/181 (89.1)
Time from trauma event to randomization, median (IQR), h	13 (8-18) [n = 184]	12 (7-18) [n = 183]

Abbreviations: GCS, Glasgow Coma Scale; ICU, intensive care unit; IQR, interquartile range.

[a] Worst value recorded between the trauma event and inclusion in the study (or before sedation).

[b] Worst response recorded between the trauma event and inclusion in the study.

[c] One or more episodes at any time between the trauma and the inclusion in the study. Hypotension was defined as systolic blood pressure less than 90 mm Hg for more than 5 minutes. Hypoxia was defined as oxygen saturation less than 92% for more than 5 minutes or Pao_2 less than 10 kPa.

[d] First brain computed tomographic (CT) scan after trauma event, assessed by unblinded investigator prior to inclusion.[27]

performed with SAS software, version 9.4 (SAS Institute Inc). No interim efficacy analysis was performed. Type I error was set at α = .05. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary outcomes should be interpreted as exploratory.

Results

Patients

From November 2017 through February 2020, 370 patients underwent randomization and were followed up for 6 months (185 patients in the intervention group and 185 in the control group). Primary outcome data were not obtained for 11 patients (3%): 4 patients refused the use of their medical data after randomization (consent withdrawal) and 7 patients were not followed up at 6 months (2 were under guardianship, 1 had no TBI, and 4 were lost to follow-up) (Figure 1). Continuous infusion of 20% hypertonic saline solution was administered for a mean of 2.7 (SD, 1.3) days in the intervention group, and no patient in the control group received this treatment as rescue therapy. Characteristics at baseline are reported in **Table 1**.

Physiological Measurements Over the First 7 Days

Comparisons of the change from day 1 to day 7 after randomization in blood osmolarity, blood sodium level, percentage of patients with intracranial hypertension, intracranial pressure, and cerebral perfusion pressure by repeated-measures analyses are shown in **Figure 2** and eFigure 3 in Supplement 2. The intervention was significantly associated with higher blood osmolarity and sodium concentration. The intervention was also significantly associated with a reduction of the risk of intracranial hypertension (OR, 0.07; 95% CI, 0.02-0.20), but there was a significant interaction between the treatment effect and time (OR, 2.50; 95% CI, 1.89-3.29) (eFigure 3 in Supplement 2), suggesting a rebound of intracranial hypertension risk after intervention discontinuation (Figure 2D). After the intervention cessation, blood osmolarity and sodium level slowly decreased, and no rebound rise in intracranial pressure was recorded during the first 48 hours (eFigure 4 in Supplement 2).

Primary Outcome

The test of the proportional odds assumption showed no significant difference in the 6-month GOS-E score distribution between the 2 groups (P = .08). Six months after the trauma, the distribution of GOS-E scores was not significantly shifted in the intervention group vs the control group (adjusted common OR, 1.02; 95% CI, 0.71-1.47; P = .92) (**Figure 3**A).

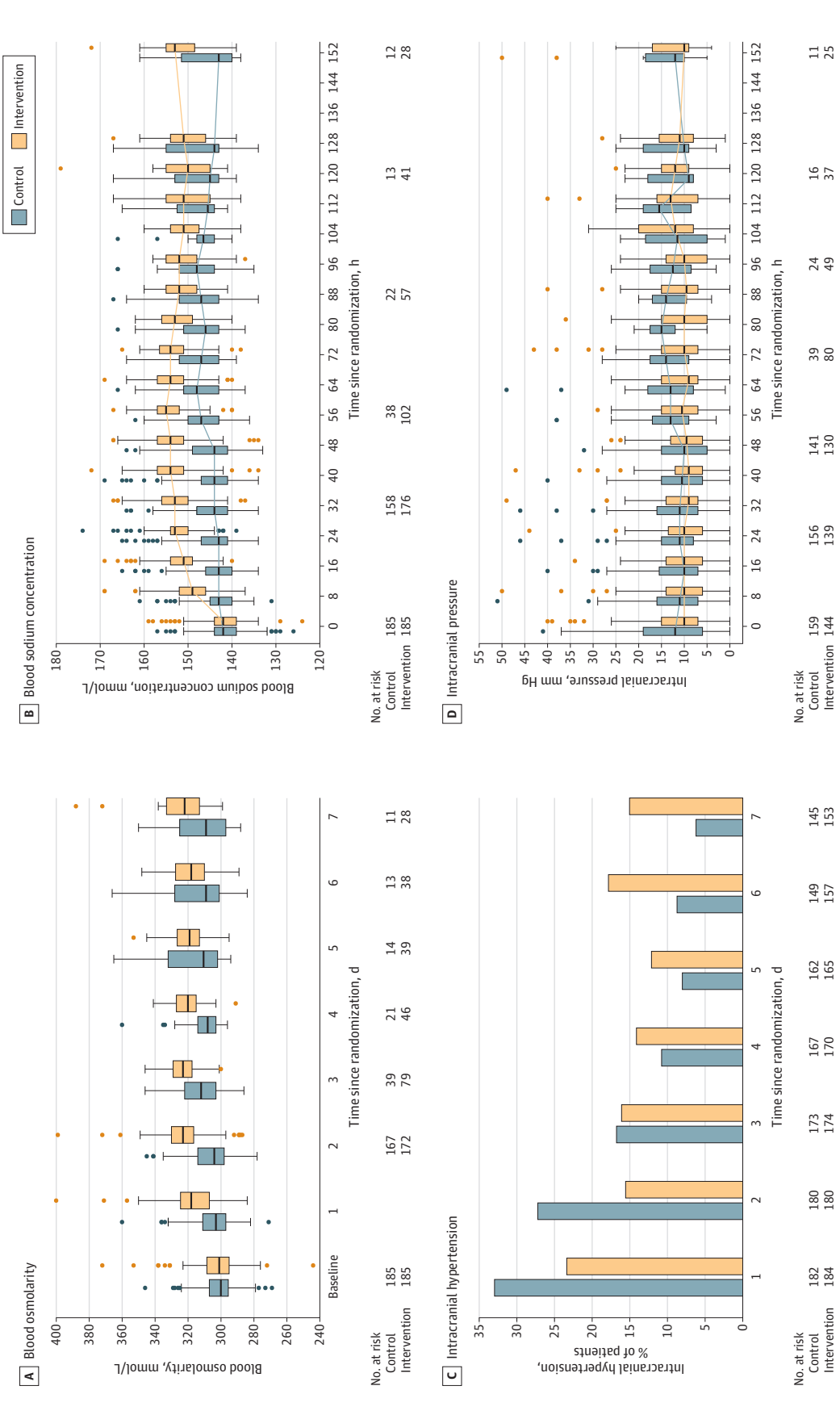
Secondary Outcomes

Intracranial hypertension episodes occurred in 62 patients (33.7%) in the intervention group and 66 patients (36.3%) in the control group (absolute difference, −2.6% [95% CI, −12.3% to 7.2%]; adjusted OR, 0.80 [95% CI, 0.51-1.26]). The frequencies and durations of therapies to control intracranial pressure (cerebrospinal fluid drainage, hypothermia, hyperventilation, barbiturates, or decompressive craniectomy) are described in eTable 1 in Supplement 2. Moderate hypocapnia was induced in 11.5% of the patients in the intervention group and 5.5% in the control group (difference, 6.1%; 95% CI, 0.3%-11.9%). The rates and durations of the other interventions were not significantly different between the study groups. The median duration of ICU stay was 16 (interquartile

© 2021 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Mexico | Access Provided by JAMA , Caro Nolasco on 10/29/2024

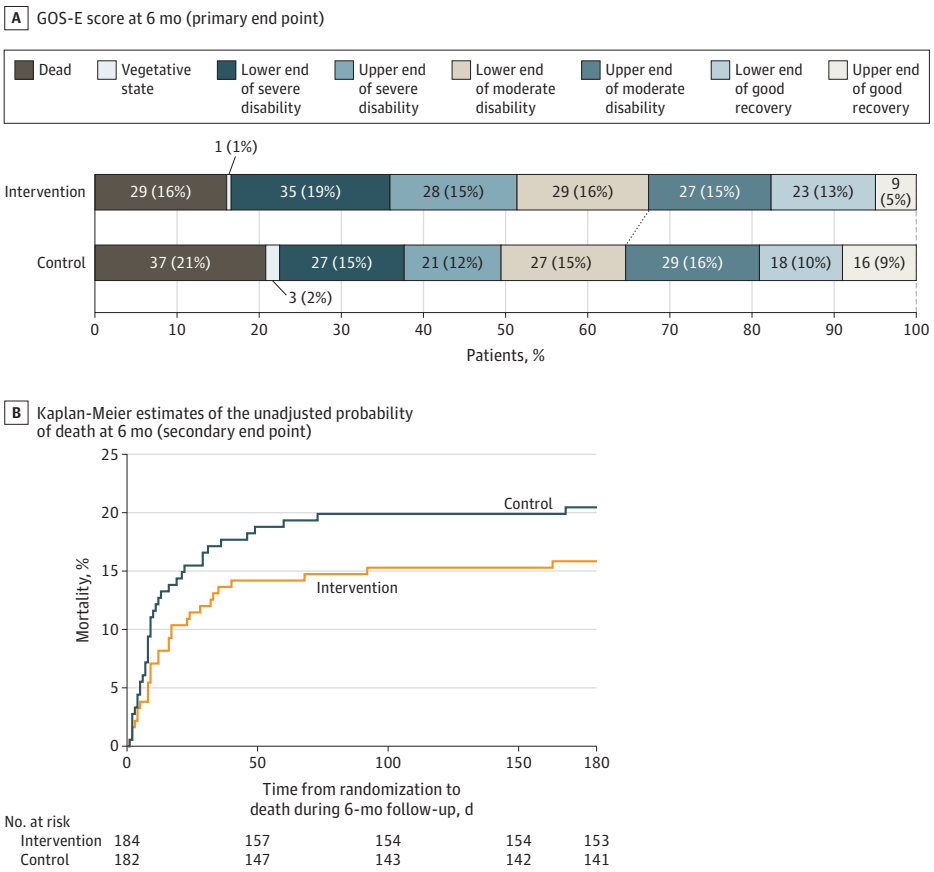
Figure 2. Physiological Measurements During the First 7 Days



Box plots show observed data (no imputation if not monitored at the indicated time). A, B, and D, Horizontal lines within boxes indicate medians; box tops and bottoms, IQR; whiskers, the furthest value within 1.5× IQR; and dots, outliers. The mean differences attributed to the treatment effects calculated by linear mixed-effects models taking into account the effects of time and treatment were 13.50 (95% CI, 10.07-16.93) mmol/L for blood osmolarity, 7.38 (95% CI, 6.35-8.41) mmol/L for blood sodium, and −1.3 (95% CI, −2.8 to 0.3) mm Hg for intracranial pressure. C, Patients without invasive intracranial pressure monitoring were considered free of intracranial hypertension. The odds ratio of the treatment effect calculated by logistic mixed-effects models accounting for time and treatment effects was 0.07 (95% CI, 0.02-0.26).

© 2021 American Medical Association. All rights reserved.
Downloaded from jamanetwork.com by Mexico | Access Provided by JAMA , Caro Nolasco on 10/29/2024

Figure 3. Outcomes at 6 Months



A, Distribution of Extended Glasgow Outcome Scale (GOS-E) scores at 6 months. Different colors correspond to GOS-E scores. The connecting line between the 2 study groups indicates the GOS-E outcome dichotomization (poor vs favorable). B, Kaplan-Meier estimates of the unadjusted probability of death at 6 months in patients receiving continuous infusion of 20% hypertonic saline solution or standard care. The estimate adjusted probability of death at 6 months is a hazard ratio of 0.79 (95% CI, 0.48-1.28). The median observation time was 180 days (interquartile range, 180-180 days) in both treatment groups. Graphical assessment indicates that the proportionality assumption was met.

range, 8-29) days in the intervention group vs 15 (interquartile range, 8-24) days in the control group (difference, 1.0 day; 95% CI, −1.0 to 4.0 days).

Favorable neurological outcomes at 6 months (GOS-E score of 6-8, indicating upper moderate disability to good recovery) occurred in 59 of 181 patients (32.6%) in the intervention group and 63 of 178 patients (35.4%) in the control group (absolute difference, −2.8% [95% CI, −12.6% to 7.0%]; adjusted OR, 0.85 [95% CI, 0.53-1.36]) (**Table 2**).

In subgroup analyses (eFigure 5 in Supplement 2), although the point estimate for the OR for favorable outcome with intervention was lower in patients with diffused injury than in those with mass lesion, the test for interaction was not statistically significant (P = .06), and TBI severity did not significantly modify the effect of the intervention (P = .30 for interaction). The treatment effect did not vary significantly across centers (P = .26 for interaction; eFigure 6 in Supplement 2), and no secular trend was observed during the inclusion period (eFigure 7 in Supplement 2). In the randomization stratum of patients, the adjusted OR was 0.72 (95% CI, 0.40-1.30) (absolute difference, −8.9%; 95% CI, −19.9% to 2.1%) in patients with severe TBI and the adjusted OR was 1.34 (95% CI, 0.54-3.36) (absolute difference, 13.2%; 95% CI, −6.3% to 32.7%) in those with moderate TBI (P = .30 for interaction). Baseline characteristics and outcomes of the subgroups of severe and moderate TBI are respectively described in eTables 2-3 and eTables 4-5 in Supplement 2.

Evaluation of disability as assessed by posttraumatic amnesia, quality of life, independence, and return home at 3 months and 6 months are described in Table 2. As assessed by the Short Form 36 at 3 and 6 months, quality of life was not significantly different between the 2 study groups (see eTable 6 in Supplement 2 for the description of all Short Form 36 dimensions). The percentages of patients alive and independent in activities of daily living at 6 months were 72.8% in the intervention group and 67.1% in the control group (absolute difference, 5.7% [95% CI, −3.8% to 15.3%]; adjusted OR, 1.30 [95% CI, 0.81-2.09]). The adjusted common OR for the distribution of GOS-E scores at 3 months was 1.27 (95% CI, 0.87-1.84) (eFigure 8 in Supplement 2). There was no significant difference in 6-month mortality (29 [15.9%] in the intervention group vs 37 [20.8%] in the control group; absolute difference, −4.9% [95% CI, −12.8% to 3.1%]; hazard ratio, 0.79 [95% CI, 0.48-1.28]) (Figure 3B).

Adverse Events

The rates of severe adverse events were 27% in the intervention group and 24.9% in the control group (**Table 3**; see eTable 7 in Supplement 2 for a complete list of severe adverse events). The rates of severe hypernatremia (sodium level >160 mmol/L)

© 2021 American Medical Association. All rights reserved.
Downloaded from jamanetwork.com by Mexico | Access Provided by JAMA , Caro Nolasco on 10/29/2024

Table 2. Secondary Outcomes

Outcomes	Intervention (n = 185)	Control (n = 185)	Absolute difference (95% CI)[a]	Odds ratio (95% CI)
Good neurological outcomes, No./total (%)[b]				
At 3 mo	62/175 (35.4)	53/176 (30.1)	5.31 (−4.49 to 15.12)	1.27 (0.79-2.06)
At 6 mo	59/181 (32.6)	63/178 (35.4)	−2.80 (−12.59 to 7.00)	0.85 (0.53-1.36)
Patients alive without posttraumatic amnesia, No./total (%)[c]				
At ICU discharge	32/179 (17.9)	24/179 (13.4)	4.47 (−3.04 to 11.98)	1.45 (0.81-2.60)
At 3 mo	56/121 (46.3)	51/130 (39.2)	7.05 (−5.17 to 19.27)	1.30 (0.77-2.20)
At 6 mo	78/139 (56.1)	66/142 (46.5)	9.64 (−2.00 to 21.27)	1.45 (0.90-2.35)
SF-36 Physical Composite Score, mean (SD)[d]				
At 3 mo	39.7 (10.3)	38.7 (10.3)	1.16 (−1.80 to 4.11)	
At 6 mo	43.7 (10.5)	43.0 (11.1)	1.12 (−1.89 to 4.11)	
SF-36 Mental Composite Score, mean (SD)[d]				
At 3 mo	39.8 (12.3)	41.2 (11.0)	−1.41 (−4.73 to 1.90)	
At 6 mo	41.6 (11.4)	43.1 (10.7)	−1.67 (−4.80 to 1.46)	
Independence, No./total (%)[e]				
At 3 mo	112/175 (64.0)	110/174(63.2)	0.78 (−9.31 to 10.88)	1.00 (0.64-1.59)
At 6 mo	131/180 (72.8)	118/176 (67.1)	5.73 (−3.78 to 15.25)	1.30 (0.81-2.09)
Return home, No./total (%)				
At 3 mo	83/179 (46.4)	76/180 (42.2)	4.15 (−6.12 to 14.41)	1.21 (0.78-1.87)
At 6 mo	106/181 (58.6)	103/178 (57.9)	0.70 (−9.51 to 10.90)	1.01 (0.65-1.57)

Abbreviation: ICU, intensive care unit.

[a] Positive differences mean that intervention group scored better than the control group.

[b] Good neurological outcome was defined as upper moderate disability to upper good recovery (Extended Glasgow Outcome Scale score of 6-8).

[c] The GOAT (Galveston Orientation & Amnesia Test) is a 10-question test that assesses temporal and spatial orientation, memory, and autobiographical recall. The score is the sum of each question, ranging from 0 to 100. A score lower than 75 signifies the persistence of posttraumatic amnesia. The GOAT was assessed and analyzed in survivors (358 patients at ICU discharge, 251 at 3 months, and 281 at 6 months).

[d] The Short Form 36 (SF-36) health survey is a 36-item, patient-reported survey of quality of life. The SF-36 is a measure of health status consisting of 8 scaled scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health). A score of 0 is equivalent to maximum disability and a score of 100 is equivalent to no disability. The SF-36 was assessed and analyzed only in survivors (202 patients at 3 months and 237 at 6 months).

[e] Defined as alive with a Katz Index of Independence in Activities of Daily Living of greater than 6. The index is the unweighted sums of 6 items: bathing, dressing, toileting, transferring, continence, and feeding. Each item is scored independently, from 0 (complete inability) to 2 (independence), and the index ranges from 0 (maximum dependence) to 12 (complete independence). An index greater than 6 was considered independence (assessed and analyzed in 285 patients at 3 months and 290 at 6 months).

were 12.4% in the intervention group and 6% in the control group, and thromboembolic events were recorded for 6% and 2.2% of patients, respectively.

Discussion

In this multicenter randomized clinical trial involving patients with moderate to severe TBI, continuous infusion of 20% hypertonic saline solution for a minimum of 48 hours did not significantly improve clinical outcome as assessed by the GOS-E measured at 6 months.

The inclusion of patients with moderate TBI may have decreased the power to demonstrate the effects of continuous infusion of hypertonic saline solution because the risk of intracranial hypertension is lower in this population. International guidelines recommend the use of broad inclusion criteria as long as they are compatible with the mechanisms of action of the evaluated intervention because this maximizes recruitment rates and improves the generalization of results.[25] The inclusion of moderate trauma, which accounts for 11% of total injuries vs 8% for severe forms,[28] increased both the representativeness of the study population and the generalizability of findings. Moreover, since 5% to 20% of patients with moderate TBI experience neurological deterioration[29] and up to 44% of patients have incomplete recovery at 6 months,[30] it was hypothesized that the benefit from the intervention could still be clinically important. A high rate of neurological sequelae was observed even with the inclusion of moderate to severe TBI, supporting the need to validate therapeutic approaches in this broad population. The prevention of hypo-osmolarity is recommended in patients with brain injury independent of the trauma severity.[6] Several of the properties of hypertonic saline solutions, such as enhancing macrocirculation and microcirculation and reducing glutamate-mediated neurotoxicity, could be beneficial to patients with moderate TBI even in the absence of intracranial hypertension.

The most recent guidelines from the Brain Trauma Foundation advocated for the performance of multicenter randomized studies evaluating hypertonic saline therapy because strong

© 2021 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Mexico | Access Provided by JAMA , Caro Nolasco on 10/29/2024

Table 3. Adverse Events

Adverse events	No. (%) Intervention (n = 185)	Control (n = 185)
Adverse effects	120 (64.9)	113 (61.1)
Severe adverse effects[a]	50 (27)	46 (24.9)
Central pontine myelinolysis[b]	1 (0.5)	1 (0.5)
Metabolic tolerance		
Severe hypernatremia (>160 mmol/L)	23 (12.4)	11 (6)
Hyponatremia (<135 mmol/L)	4 (2.2)	3 (1.6)
Hypokalemia (<3 mmol/L)	0	0
Acute kidney injury (KDIGO stage ≥2)[c]	4 (2.2)	8 (4.4)
Deep vein thrombosis or pulmonary embolism	11 (6)	4 (2.2)
Hospital-acquired pneumonia	83 (44.9)	75 (40.5)

Abbreviation: KDIGO, Kidney Disease: Improving Global Outcomes.

[a] Defined as adverse events that result in death, prolongation of hospitalization, or persistent or significant disability or incapacity or is medically important as defined by the European Medicines Agency. Expected and unexpected serious adverse events were reported in a blinded manner to the sponsor for central validation of severity level.

[b] Diagnosis confirmed on magnetic resonance imaging.

[c] KDIGO stage 2 or higher based on elevated serum creatinine, reduced urine output, and in some cases, initiation of kidney replacement therapy.

evidence is lacking to support any specific recommendation.[5] In this setting, using mortality as a primary outcome is not recommended because a strategy that decreases mortality at the cost of poor neurological outcomes would not be recommended. Among the assessments investigating dependence or quality of life after TBI, the GOS-E is the best validated assessment for a telephone evaluation during a structured interview[21] and has been widely used in recent clinical trials.[18,23,31]

The intervention was associated with a lower risk of intracranial hypertension during the first 2 days, and a rebound of intracranial hypertension was apparent from day 4 onward. Because the mean duration of the intervention was 2.7 (SD, 1.3) days, discontinuation of the infusion of hypertonic solution may be an important step to prevent secondary brain injury. The risk of rebound is potentially due to the intracellular accumulation of organic osmolytes in brain tissue, which could cause rebound brain swelling during normalization of serum sodium, with the osmotic gradient favoring free water entry into the brain tissue.[16] The study protocol planned a 48-hour follow-up of sodium blood level to maintain sodium above 140 mmol/L after intervention discontinuation, but the blood sodium levels were not normalized at the end of this monitoring period. After intervention, the time to reach normal natremia and the duration of monitoring likely needs to be adapted to the individual evolution of brain swelling.

The type of fluid used is critical when interpreting the effects of continuous administration of hypertonic solutions. The use of hypertonic saline or mannitol as a bolus of hyperosmolar therapy is controversial because neither has been proven to improve clinical outcomes in high-quality clinical trials.[32,33] Mannitol administration has never been reported as a continuous infusion, probably due to the risk of severe metabolic disturbance. For continuous infusion of hypertonic saline solution, chloride-rich or lactate-rich solutions have been tested, but similar effects on ICU survival were noted in a systematic review.[13] The concentrations of hypertonic chloride sodium, which varied from 2% to 23.4% in other studies in neuro-ICUs,[34] could also alter the effect of the intervention. A 20% saline solution was used in this study to limit the fluid volume, because fluid retention is one of the most frequent adverse events reported with hypertonic therapies. The investigation of the dose-effect relationship of the intervention would be of interest to define the most effective therapy for future trials.

Concerns about hypertonic saline solution safety, including neurological complications, kidney toxicity, and thromboembolic events, have hindered its use in clinical practice. Except for the risk of severe hypernatremia, the rates of severe adverse effects were similar in the 2 study groups. Spontaneous severe hypernatremia has been associated with the risk of death in general critically ill patients[35] and after TBI.[36] No increase in the risk of death was observed with the intervention. The standardized close biological monitoring for dose adaptation was likely critical in limiting the risk of adverse events. It has also been proposed that the greatest risk of continuous hyperosmolar infusions is progressive salt and water overload, increasing the risk of delayed intracranial hypertension when resuscitation fluids are being normally mobilized. Accordingly, the effect of the treatment on the rates of intracranial hypertension varied with the time. Contrary to what has been observed in critically ill patients,[37,38] the high load of sodium chloride administered in the intervention group was not associated with acute kidney injury. This discrepancy could be explained by the frequent increase in renal clearance in trauma patients, which could increase the tolerance of chloride saline solutions.[39]

Limitations

This study has several limitations. First, many patients in the control group received a bolus of hyperosmolar therapy, reflecting standard care. It could be considered unethical to not administer a bolus of hyperosmolar therapy in the control group. No patient in the control group received continuous hyperosmolar therapy, and a significant difference in blood osmolality was observed between the 2 groups. Second, blinding of the intervention was not possible. To limit the risk of bias, GOS-E scores were estimated centrally by trained, blinded outcome assessors. Third, although some patients developed intracranial hypertension between randomization and the study intervention initiation, the present trial did not examine the effectiveness of a curative therapy but rather prevention. Fourth, the percentage of patients developing intracranial hypertension and the levels of intracranial pressure were not reduced by the intervention. However, the interpretation of these intermediate end points can be confounded in patients who are managed with aggressive critical care for intracranial pressure control. The comparison of the therapeutic intensity level between the 2 study groups would have strengthened these observations.[40]

© 2021 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Mexico | Access Provided by JAMA , Caro Nolasco on 10/29/2024

Conclusions

Among patients with moderate to severe traumatic brain injury, treatment with continuous infusion of 20% hypertonic saline compared with standard care did not result in a significantly better neurological status at 6 months. However, confidence intervals for the findings were wide, and the study may have had limited power to detect a clinically important difference.

ARTICLE INFORMATION

Accepted for Publication: March 25, 2021.

Author Affiliations: Université de Nantes, CHU Nantes, Pôle anesthésie réanimations, Service d'Anesthésie Réanimation chirurgicale, Hôtel Dieu, Nantes, France (Roquilly, Cinotti, Demeure dit Latte, Mahe, Vourc'h, Martin, Chopin, Lerebourg, Asehnoune); Department of Anesthesiology and Critical Care, Beaujon Hospital, DMU Parabol, AP-HP Nord, Paris, France (Moyer, Jeantrelle); CHU de Brest, Anesthesia and Intensive Care Unit, Brest, France (Huet, Vermeersch); CHU d'Angers, Anesthesia and Intensive Care Unit, Angers, France (Lasocki, Gaillard); CHU de Tours, Anesthesia and Intensive Care Unit, Tours, France (Cohen); CHU de Potiers, Anesthesia and Intensive Care Unit, Poitiers, France (Dahyot-Fizelier); CHU de Montpellier, Anesthesia and Intensive Care Unit, Montpellier, France (Chalard); CHU de Rennes, Anesthesia and Intensive Care Unit, Rennes, France (Seguin); CHU de Nantes, Service de pharmacie, Hôtel Dieu, Nantes, France (Flet); DRCI, Departement promotion, cellule vigilances, CHU Nantes, Nantes, France (Chiffoleau); DRCI, Plateforme de Méthodologie et de Biostatistique, CHU Nantes, Nantes, France (Feuillet); Université de Nantes, Université de Tours, INSERM, SPHERE U1246, Nantes, France (Feuillet).

Author Contributions: Dr Roquilly had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Roquilly, Demeure dit Latte, Mahe, Vourc'h, Flet, Feuillet, Asehnoune.
Acquisition, analysis, or interpretation of data: Roquilly, Moyer, Huet, Lasocki, Cohen, Dahyot-Fizelier, Chalard, Seguin, Jeantrelle, Vermeersch, Gaillard, Cinotti, Demeure dit Latte, Vourc'h, Martin, Chopin, Lerebourg, Chiffoleau, Feuillet.
Drafting of the manuscript: Roquilly, Chalard, Vermeersch, Cinotti, Vourc'h, Feuillet, Asehnoune.
Critical revision of the manuscript for important intellectual content: Moyer, Huet, Lasocki, Cohen, Dahyot-Fizelier, Seguin, Jeantrelle, Gaillard, Demeure dit latte, Mahe, Vourc'h, Martin, Chopin, Lerebourg, Flet, Chiffoleau, Asehnoune.
Statistical analysis: Feuillet.
Obtained funding: Roquilly.
Administrative, technical, or material support: Vermeersch, Cinotti, Demeure dit Latte, Vourc'h, Martin, Chopin, Lerebourg, Flet, Chiffoleau.
Supervision: Roquilly, Asehnoune.

Conflict of Interest Disclosures: Dr Roquilly reported receiving grants and consulting fees from Merck and bioMérieux. Dr Cinotti reported receiving personal fees from Paion. Dr Asehnoune reported receiving lecture fees from Baxter, Fisher & Paykel, and LFB and consulting fees from Edwards Lifesciences and LFB. No other disclosures were reported.

Funding/Support: This study was supported by a grant from the French Ministry of Health Programme Hospitalier de Recherche Clinique Inter-regional 2016 (PHRCI 2016, RC16_0474). The Nantes University Hospital acted as the sponsor of the study.

Role of the Funder/Sponsor: The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Group Information: The members of the Atlanrea Study Group and the Société Française d'Anesthésie Réanimation (SFAR) Research Network appear in Supplement 4.

REFERENCES

1. Dewan MC, Rattani A, Gupta S, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg*. 2018;130(4):1-18. doi:10.3171/2017.10.jns17352

2. James SL, Theadom A, Ellenbogen RG, et al; GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(1):56-87. doi:10.1016/S1474-4422(18)30415-0

3. Steyerberg EW, Wiegers E, Sewalt C, et al; CENTER-TBI Participants and Investigators. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. *Lancet Neurol*. 2019;18(10):923-934. doi:10.1016/S1474-4422(19)30232-7

4. Maas AIR, Menon DK, Adelson PD, et al; InTBIR Participants and Investigators. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol*. 2017;16(12):987-1048. doi:10.1016/S1474-4422(17)30371-X

5. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery*. 2017;80(1):6-15. doi:10.1227/neu.0000000000001432

6. Oddo M, Poole D, Helbok R, et al. Fluid therapy in neurointensive care patients: ESICM consensus and clinical practice recommendations. *Intensive Care Med*. 2018;44(4):449-463. doi:10.1007/s00134-018-5086-z

7. Tan SKR, Kolmodin L, Sekhon MS, et al. The effect of continuous hypertonic saline infusion and hypernatremia on mortality in patients with severe traumatic brain injury: a retrospective cohort study [in French]. *Can J Anaesth*. 2016;63(6):664-673. doi:10.1007/s12630-016-0633-y

8. Froelich M, Ni Q, Wess C, Ougorets I, Härtl R. Continuous hypertonic saline therapy and the occurrence of complications in neurocritically ill patients. *Crit Care Med*. 2009;37(4):1433-1441. doi:10.1097/CCM.0b013e31819c1933

9. Hauer E-M, Stark D, Staykov D, Steigleder T, Schwab S, Bardutzky J. Early continuous hypertonic saline infusion in patients with severe cerebrovascular disease. *Crit Care Med*. 2011;39(7):1766-1772. doi:10.1097/CCM.0b013e318218a390

10. Wagner I, Hauer E-M, Staykov D, et al. Effects of continuous hypertonic saline infusion on perihemorrhagic edema evolution. *Stroke*. 2011;42(6):1540-1545. doi:10.1161/STROKEAHA.110.609479

11. Roquilly A, Mahe PJ, Latte DDD, et al. Continuous controlled-infusion of hypertonic saline solution in traumatic brain-injured patients: a 9-year retrospective study. *Crit Care*. 2011;15(5):R260. doi:10.1186/cc10522

12. Ichai C, Payen J-F, Orban J-C, et al. Half-molar sodium lactate infusion to prevent intracranial hypertensive episodes in severe traumatic brain injured patients: a randomized controlled trial. *Intensive Care Med*. 2013;39(8):1413-1422. doi:10.1007/s00134-013-2978-9

13. Asehnoune K, Lasocki S, Seguin P, et al; ATLANREA Group; COBI Group. Association between continuous hyperosmolar therapy and survival in patients with traumatic brain injury—a multicentre prospective cohort study and systematic review. *Crit Care*. 2017;21(1):328. doi:10.1186/s13054-017-1918-4

14. Roquilly A, Lasocki S, Moyer JD, et al; COBI Group. COBI (Continuous Hyperosmolar Therapy for Traumatic Brain-Injured Patients) trial protocol: a multicentre randomised open-label trial with blinded adjudication of primary outcome. *BMJ Open*. 2017;7(9):e018035. doi:10.1136/bmjopen-2017-018035

15. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

16. Adrogué HJ, Madias NE. Hypernatremia. *N Engl J Med*. 2000;342(20):1493-1499. doi:10.1056/NEJM200005183422006

17. Geeraerts T, Velly L, Abdennour L, et al; French Society of Anaesthesia; Intensive Care Medicine; Association de Neuro-Anesthésie-Réanimation de Langue Française (Anarlf); French Society of Emergency Medicine (Société Française de Médecine d'Urgence (SFMU); Société Française de Neurochirurgie (SFN); Groupe Francophone de Réanimation et d'Urgences Pédiatriques (GFRUP); Association des Anesthésistes-Réanimateurs Pédiatriques d'Expression Française (Adarpef). Management of severe traumatic brain injury (first 24 hours). *Anaesth Crit Care Pain Med*. 2018;37(2):171-186. doi:10.1016/j.accpm.2017.12.001

18. Nichol A, French C, Little L, et al; EPO-TBI Investigators; ANZICS Clinical Trials Group. Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial. *Lancet*. 2015;386(10012):2499-2506. doi:10.1016/S0140-6736(15)00386-4

© 2021 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Mexico | Access Provided by JAMA , Caro Nolasco on 10/29/2024

19. Pettigrew LEL, Wilson JTL, Teasdale GM. Reliability of ratings on the Glasgow Outcome Scales from in-person and telephone structured interviews. *J Head Trauma Rehabil*. 2003;18(3):252-258. doi:10.1097/00001199-200305000-00003

20. Fayol P, Carrière H, Habonimana D, Preux P-M, Dumond J-J. French version of structured interviews for the Glasgow Outcome Scale: guidelines and first studies of validation [in French]. *Ann Readapt Med Phys*. 2004;47(4):142-156. doi:10.1016/j.annrmp.2004.01.004

21. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: guidelines for their use. *J Neurotrauma*. 1998;15(8):573-585. doi:10.1089/neu.1998.15.573

22. Roozenbeek B, Lingsma HF, Perel P, et al; IMPACT Study Group; CRASH Trial Collaborators. The added value of ordinal analysis in clinical trials: an example in traumatic brain injury. *Crit Care*. 2011;15(3):R127. doi:10.1186/cc10240

23. Andrews PJD, Sinclair HL, Rodriguez A, et al; Eurotherm3235 Trial Collaborators. Hypothermia for intracranial hypertension after traumatic brain injury. *N Engl J Med*. 2015;373(25):2403-2412. doi:10.1056/NEJMoa1507581

24. Hutchinson PJ, Kolias AG, Timofeev IS, et al; RESCUEicp Trial Collaborators. Trial of decompressive craniectomy for traumatic intracranial hypertension. *N Engl J Med*. 2016;375(12):1119-1130. doi:10.1056/NEJMoa1605215

25. Maas AIR, Steyerberg EW, Marmarou A, et al. IMPACT recommendations for improving the design and analysis of clinical trials in moderate to severe traumatic brain injury. *Neurotherapeutics*. 2010;7(1):127-134. doi:10.1016/j.nurt.2009.10.020

26. Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS Med*. 2008;5(8):e165. doi:10.1371/journal.pmed.0050165

27. Marshall LF, Marshall SB, Klauber MR, et al. The diagnosis of head injury requires a classification based on computed axial tomography. *J Neurotrauma*. 1992;9(9)(suppl 1):S287-S292.

28. Peeters W, van den Brande R, Polinder S, et al. Epidemiology of traumatic brain injury in Europe. *Acta Neurochir (Wien)*. 2015;157(10):1683-1696. doi:10.1007/s00701-015-2512-7

29. Bouzat P, Almeras L, Manhes P, et al; TBI-TCD Study Investigators. Transcranial Doppler to predict neurologic outcome after mild to moderate traumatic brain injury. *Anesthesiology*. 2016;125(2):346-354. doi:10.1097/ALN.0000000000001165

30. Watanitanon A, Lyons VH, Lele AV, et al. Clinical epidemiology of adults with moderate traumatic brain injury. *Crit Care Med*. 2018;46(5):781-787. doi:10.1097/CCM.0000000000002991

31. Cooper DJ, Nichol AD, Bailey M, et al; POLAR Trial Investigators and ANZICS Clinical Trials Group. Effect of early sustained prophylactic hypothermia on neurologic outcomes among patients with severe traumatic brain injury: the POLAR randomized clinical trial. *JAMA*. 2018;320(21):2211-2220. doi:10.1001/jama.2018.17075

32. Rowland MJ, Veenith T, Hutchinson PJ, Perkins GD; SOS Trial Investigators. Osmotherapy in traumatic brain injury. *Lancet Neurol*. 2020;19(3):208. doi:10.1016/S1474-4422(20)30003-X

33. Kamel H, Navi BB, Nakagawa K, Hemphill JC III, Ko NU. Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: a meta-analysis of randomized clinical trials. *Crit Care Med*. 2011;39(3):554-559. doi:10.1097/CCM.0b013e318206b9be

34. Tyagi R, Donaldson K, Loftus CM, Jallo J. Hypertonic saline: a clinical review. *Neurosurg Rev*. 2007;30(4):277-289. doi:10.1007/s10143-007-0091-7

35. Darmon M, Timsit J-F, Francais A, et al. Association between hypernatraemia acquired in the ICU and mortality: a cohort study. *Nephrol Dial Transplant*. 2010;25(8):2510-2515. doi:10.1093/ndt/gfq067

36. Maggiore U, Picetti E, Antonucci E, et al. The relation between the incidence of hypernatremia and mortality in patients with severe traumatic brain injury. *Crit Care*. 2009;13(4):R110. doi:10.1186/cc7953

37. Semler MW, Self WH, Wanderer JP, et al; SMART Investigators and Pragmatic Critical Care Research Group. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med*. 2018;378(9):829-839. doi:10.1056/NEJMoa1711584

38. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA*. 2012;308(15):1566-1572. doi:10.1001/jama.2012.13356

39. Udy AA, Roberts JA, Shorr AF, Boots RJ, Lipman J. Augmented renal clearance in septic and traumatized patients with normal plasma creatinine concentrations: identifying at-risk patients. *Crit Care*. 2013;17(1):R35. doi:10.1186/cc12544

40. Zuercher P, Groen JL, Aries MJH, et al. Reliability and validity of the therapy intensity level scale: analysis of clinimetric properties of a novel approach to assess management of intracranial pressure in traumatic brain injury. *J Neurotrauma*. 2016;33(19):1768-1774. doi:10.1089/neu.2015.4266

© 2021 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Mexico | Access Provided by JAMA , Caro Nolasco on 10/29/2024